Applying MedDRA® in Clinical Safety and Pharmacovigilance

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Learning Objectives

• Describe how to code clinical safety data accurately and consistently with MedDRA
• Apply the principles described in the ICH-endorsed “MedDRA Term Selection: Points to Consider” document
• Review the various strategies for retrieval and subsequent analysis of MedDRA-coded data in clinical safety and pharmacovigilance
• Discuss the methodologies of MedDRA versioning
Tutorial Overview

• Overview of MedDRA
• Coding and the “MedDRA Term Selection: Points to Consider” document
  – Data quality issues and coding exercises
• MedDRA’s application in data retrieval and analysis: the “MedDRA Data Retrieval and Presentation: Points to Consider” document
  – Query development exercise
  – Standardised MedDRA Queries (SMQs)
  – Customized searches
  – FDA approach to MedDRA search strategy for signal detection: examples from FDA FAERS database and New Drug Safety Review
• MedDRA versioning

MedDRA Training Videos

• At the MSSO Web:
  – MedDRA Structure and Scope – available in Chinese
  – Standardised MedDRA Queries (SMQs) – available in Chinese
  – Primary System Organ Class (SOC) Allocation in MedDRA
  – Introduction to the Points to Consider Documents
  – MedDRA Version Updates
Overview of MedDRA

Why MedDRA?

ICH initiative (M1)

- An international multi-lingual terminology
- Standardized communication between industry and regulators
- Support of electronic submissions
- Application throughout regulatory process for medical products
- Classification for a wide range of clinical information
- Global ICH-endorsed “Points to Consider” documents
- Global version synchronization
MedDRA Definition

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

Scope of MedDRA

- Medical conditions
- Indications
- Investigations (tests, results)
- Medical and surgical procedures
- Medical, social, family history
- Medication errors
- Product quality issues
- Device-related issues
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries

- Not a drug dictionary
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary

Patient demographic terms

Clinical trial study design terms
Which of these concepts can be coded using MedDRA®?

- Contraception
- Quadruple bypass
- Grade 3
- Social drinking
- High potassium
- Flutter valve device
- Injection site pain
- Off-label use
- Abnormal MRI
- Pharmacist dispensed wrong medication
- Amoxicillin
- Rheumatoid arthritis
- Hispanic
- Hyperactive reflexes
Applications of MedDRA in Clinical Safety and Pharmacovigilance

- Clinical trial databases (adverse events, medical & social history, investigations etc.)
- Investigator’s Brochures
- Company Core Safety Information
- Safety summaries
- Clinical Study Reports
- Individual Case Safety Reports
- Periodic Safety Update Reports
- Product Labeling

MedDRA Structure

系统器官分类 (SOC) (26)

高位组语 (HLGT) (334)

高位语 (HLT) (1,717)

首选语 (PT) (20,057)

低位语 (LLT) (71,326)
系统器官分类

- 血液及淋巴系统疾病
- 心脏器官疾病
- 各种先天性家族性遗传性疾病
- 耳及迷路类疾病
- 内分泌系统疾病
- 眼器官疾病
- 胃肠系统疾病
- 全身性疾病及给药部位各种反应
- 肝胆系统疾病
- 免疫系统疾病
- 感染及侵染类疾病
- 各类损伤、中毒及手术并发症
- 各类检查
- 代谢及营养类疾病
- 各种肌肉骨骼及结缔组织疾病
- 良性、恶性及性质不明的肿瘤（包括囊状和息肉状）
- 各类神经系统疾病
- 妊娠期、产褥期及围产期状况
- 精神病类
- 肾脏及泌尿系统疾病
- 生殖系统及乳腺疾病
- 呼吸系统、胸及纵隔疾病
- 皮肤及皮下组织类疾病
- 社会环境
- 各种手术及医疗操作
- 血管与淋巴管类疾病

MedDRA Characteristics

- Non-current LLTs
- MedDRA codes
- 多轴性
  - Single axial SOCs
- Rules for primary SOC (主SOC) allocation
  1st: 各种先天性家族性遗传性疾病
  2nd: 良性、恶性及性质不明的肿瘤（包括囊状和息肉状）
  3rd: 感染及侵染类疾病
  4th: Primary site of manifestation
Exercise – Primary SOC Rule (cont)

Which SOC is the primary? Secondary SOCs?

- PT 骨痛
- PT 肾衰
- PT 色盲
- PT 甲型肝炎
- PT 脑膜炎球菌性脑炎
- PT 甲状腺良性肿瘤
- PT 齿龈息肉
- PT 先天性人免疫缺陷病毒感染
- PT 先天性视网膜母细胞瘤

Conditions vs. Investigations

<table>
<thead>
<tr>
<th>PT</th>
<th>HLT</th>
<th>HLGT</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test positive</td>
<td>Reproductive hormone analyses</td>
<td>Endocrine investigations (incl sex hormones)</td>
<td>Investigations</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Normal pregnancy, labour and delivery</td>
<td>Pregnancy, labour and postpartum conditions</td>
<td>Pregnancy, puerperium and perinatal conditions</td>
</tr>
</tbody>
</table>
Condition or Investigation?

- 血葡萄糖高 → INV
- 高转氨酶血症 → COND
- X 线胸片显现阴影 → INV
- 胳膊上有棕色斑疹 → COND
- 呼吸率升高 → INV
- 高血压 → COND

*Exception to the rule; layperson’s term for hypertension*
Browser Demonstration

SOC View and Search

“MedDRA Term Selection: Points to Consider” Document
Why Do We Need Coding Conventions?

- Differences in medical aptitude of coders
- Consistency concerns (many more “choices” to manually code terms in MedDRA compared to older terminologies)
- Even with an autoencoder, will still need manual coding

MedDRA Term Selection: Points to Consider (MTS:PTC)

- An ICH-endorsed guide for MedDRA users
- Developed to promote medically accurate and consistent use of MedDRA in exchange of data (ultimately, for “medically meaningful” retrieval and analysis)
MedDRA Term Selection: PTC (cont)

• In some cases with more than one option for selecting terms, a “preferred option” is identified but this does not limit MedDRA users to applying that option. Organizations should be consistent in their choice of option.

• Section 4.1 – Versioning (Appendix)
  - 4.1.1 Versioning methodologies
  - 4.1.2 Timing of version implementation

General Term Selection Principles

• Quality of Source Data
• Quality Assurance
• Do Not Alter MedDRA
• Always Select a Lowest Level Term
• Select Only Current Lowest Level Terms
• When to Request a Term
• Use of Medical Judgment in Term Selection
• Selecting More than One Term
• Check the Hierarchy
• Select Terms for All Reported Information, Do Not Add Information
Select Terms for All Reported Information

- Select terms for every AR/AE reported, regardless of causal association
- Select terms for device-related events, product quality issues, medication errors, medical and social history, investigations and indications as appropriate
- If diagnosis reported with characteristic signs and symptoms, preferred option is to select term for diagnosis only

Do Not Alter MedDRA

- MedDRA is a standardized terminology with a pre-defined term hierarchy
- Users must not make *ad hoc* structural alterations, including changing the primary SOC allocation
- If terms are incorrectly placed, submit a change request to the MSSO
Synonym Lists

- Can be derived from existing term lists or directly from verbatims
- For recurring, but unusual, verbatims – one-time assignment to a MedDRA term
- Enforces consistency by limiting choices once MedDRA term is assigned
- Increases likelihood of autoencoding “hit”
- Natural outgrowth of a legacy data conversion
- Maintenance required

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Synonym List Examples

<table>
<thead>
<tr>
<th>Verbatim</th>
<th>LLT</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing above temple</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Aching all over head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsing pain in head</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular pain in legs</td>
<td>Myalgia of lower extremities</td>
<td>LLT <em>Myalgia of lower extremities</em> is a better choice than LLT <em>Muscular pain</em> since it captures both the event and body site</td>
</tr>
</tbody>
</table>
Always Select a Lowest Level Term

- Lowest Level Term that most accurately reflects the reported verbatim information should be selected
- Degree of specificity may be challenging
  - Example: “Abscess on face” → select “Facial abscess,” not simply “Abscess”

Term Selection Points

- Diagnoses and Provisional Diagnoses with or without Signs and Symptoms
- Death and Other Patient Outcomes
- Suicide and Self-Harm
- Conflicting/Ambiguous/Vague Information
- Combination Terms
- Age vs. Event Specificity
- Body Site vs. Event Specificity
- Location Specific vs. Microorganism Specific Information
- Modification of Pre-existing Conditions
- Exposures During Pregnancy and Breast Feeding
- Congenital Terms
- Neoplasms
- Medical and Surgical Procedures
- Investigations
Term Selection Points (cont)

- Medication/Administration Errors, Accidental Exposures and Occupational Exposures
- Misuse, Abuse and Addiction
- Transmission of Infectious Agent via Product
- Overdose, Toxicity and Poisoning
- Device-related Terms
- Drug Interactions
- No Adverse Effect and “Normal” Terms
- Unexpected Therapeutic Effect
- Modification of Effect
- Social Circumstances
- Medical and Social History
- Indication for Product Use
- Off Label Use
- Product Quality Issues

Diagnoses and Provisional Diagnoses

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single diagnosis without signs and symptoms</td>
<td>Single provisional diagnosis without signs and symptoms</td>
<td>Provisional diagnosis (only possible option)</td>
</tr>
<tr>
<td>• Diagnosis (only possible option)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example: &quot;Myocardial infarction&quot; → select &quot;Myocardial infarction&quot;</td>
<td>Example: &quot;Possible myocardial infarction&quot; → select &quot;Myocardial infarction&quot; (select term as if definitive diagnosis)</td>
<td></td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses
### Diagnoses and Provisional Diagnoses (cont)

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITIVE DIAGNOSIS</strong></td>
</tr>
<tr>
<td>Single diagnosis with signs/symptoms</td>
</tr>
<tr>
<td>•Preferred: Diagnosis only</td>
</tr>
</tbody>
</table>

Example: "*Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm*" → select "**Anaphylactic reaction**".

Example: "*Possible myocardial infarction with chest pain, dyspnea, diaphoresis*" → select "**Myocardial infarction**", "**Chest pain**", "**Dyspnea**", and "**Diaphoresis**".

Similar principles apply for multiple diagnoses.
Medication Errors
See Appendix B of MedDRA Introductory Guide for Concept Descriptions
“Top-down” navigation in HLGT *Medication errors* is best approach for term selection

- Medication error with clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was administered wrong drug and experienced hypotension</td>
<td>Wrong drug administered Hypotension</td>
</tr>
<tr>
<td>Because of similar sounding drug names, the patient took the wrong drug and experienced a rash</td>
<td>Drug name confusion Wrong drug administered Rash</td>
</tr>
</tbody>
</table>

Medication Errors (cont)
Important to record occurrence or potential occurrence of medication error

- Medication error without clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication was given intravenously instead of intramuscularly without sequelae</td>
<td>Intramuscular formulation administered by other route No adverse effect</td>
<td>If specifically reported that there is no adverse effect, acceptable to select LLT <em>No adverse effect</em></td>
</tr>
<tr>
<td>Pharmacist notices that the names of two drugs are similar and is concerned that this may result in a medication error</td>
<td>Circumstance or information capable of leading to medication error</td>
<td>LLT Drug name confusion could be an optional additional term to select. Note: this example is a potential medication error.</td>
</tr>
</tbody>
</table>
**Overdose, Toxicity and Poisoning**

If overdose, poisoning or toxicity is explicitly reported, select the appropriate term

- Overdose with clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach upset from study drug overdose</td>
<td>Stomach upset</td>
</tr>
<tr>
<td></td>
<td>Overdose</td>
</tr>
</tbody>
</table>

- Overdose without clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient received an overdose of medicine</td>
<td>Overdose</td>
<td>LLT No adverse effect can also be selected</td>
</tr>
<tr>
<td>without any adverse consequences</td>
<td>No adverse effect</td>
<td></td>
</tr>
</tbody>
</table>

**Misuse, Abuse and Addiction**

**New MTS:PTC Section**

3.16 – Misuse, Abuse and Addiction

The concepts of misuse, abuse and addiction are closely related and can pose challenges for term selection since the terms may overlap to some extent; the specific circumstances of each case/reported event may help in consideration for term selection of these concepts. Medical judgment and regional regulatory considerations need to be applied.

It may also be useful to consider these concepts as shown in the table below.

<table>
<thead>
<tr>
<th>Concept</th>
<th>Intentional?</th>
<th>By Whom?</th>
<th>Therapeutic Use?</th>
<th>Additional Sections in this Document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misuse</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>Yes</td>
<td>3.16.1</td>
</tr>
<tr>
<td>Abuse</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>No</td>
<td>3.16.2</td>
</tr>
<tr>
<td>Addiction</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>No</td>
<td>3.16.3</td>
</tr>
<tr>
<td>Medication error</td>
<td>No</td>
<td>Patient/consumer or healthcare provider</td>
<td>Yes</td>
<td>3.15</td>
</tr>
<tr>
<td>Off label use</td>
<td>Yes</td>
<td>Healthcare provider</td>
<td>Yes</td>
<td>3.27</td>
</tr>
</tbody>
</table>
Which option would you select using the PTC preferred approach? (cont)

• “Skin pain and blistering, possibly poison oak from patient history”
  a) LLT *Poison oak rash*
  b) LLT *Pain of skin*, LLT *Blistering*
  c) LLT *Skin disorder*
  d) LLT *Pain of skin*, LLT *Blistering*, LLT *Poison oak rash*

Which option would you select using the PTC preferred approach?

• “Skin pain and blistering, possibly poison oak from patient history”
  a) LLT *Poison oak rash*
  b) LLT *Pain of skin*, LLT *Blistering*
  c) LLT *Skin disorder*
  d) LLT *Pain of skin*, LLT *Blistering*, LLT *Poison oak rash* (select provisional diagnosis and signs/symptoms)
Which option would you select?

• “Toddler opened ‘child-proof’ cap on cough syrup bottle, drank it all, then threw up.”
  a) LLT *Failure of child resistant mechanism for pharmaceutical product*
  b) LLT *Intentional overdose, LLT Vomited*
  c) LLT *Failure of child resistant mechanism for pharmaceutical product, LLT Accidental drug intake by child, LLT Vomited*
  d) LLT *Accidental drug intake by child*
Which option would you select?

- “Toddler opened ‘child-proof’ cap on cough syrup bottle, drank it all, then threw up.
  a) LLT *Failure of child resistant mechanism for pharmaceutical product*
  b) LLT *Intentional overdose, LLT Vomited*
  c) LLT *Failure of child resistant mechanism for pharmaceutical product, LLT Accidental drug intake by child, LLT Vomited* (select terms for product quality issue, medication error, and AE)
  d) LLT *Accidental drug intake by child*

Coding Examples
Verbatim

• Lab results indicate an increase in erythrocytes.
  ◦ Assess the verbatim
  ◦ Identify the information to code
  ◦ Browse and search in MedDRA
  ◦ Select the best match LLT

• LLT ________________

Verbatim (cont)

• A three year old boy was admitted for loratadine toxicity after accidentally ingesting the remaining tablets in the bottle.
Verbatim (cont)

- Sepsis leading to shock from possible spontaneous bacterial peritonitis or bowel perforation

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>Unspecified neurological condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Small perforation of colon after colonoscopy</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Elderly woman complained her arm was tender where she had received her seasonal flu vaccine</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Influenza with body aches, fever, cough</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>72 year old man with aphasia and right hemiplegia. Rule out stroke in middle cerbral artery territory.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Fetus was inadvertently exposed to radiation (mother had X-ray not knowing she was pregnant)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Baby born with intestinal obstruction</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Large tumour in brain</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Recurrence of hepatic cancer</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Cartilage removed left knee</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Thrombocytopenia with decreased platelet count</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Doctor prescribed wrong dose of drug X</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>13</strong></td>
<td>Interventional radiologist exposed to radiation over many years</td>
<td></td>
</tr>
<tr>
<td><strong>14</strong></td>
<td>Patient deliberately took drug X twice a day instead of once a day as prescribed</td>
<td></td>
</tr>
<tr>
<td><strong>15</strong></td>
<td>Addicted to heroin</td>
<td></td>
</tr>
<tr>
<td><strong>16</strong></td>
<td>Patient deliberately took overdose of several drugs</td>
<td></td>
</tr>
<tr>
<td><strong>17</strong></td>
<td>Patient complained that nasogstric tube was irritating her</td>
<td></td>
</tr>
<tr>
<td><strong>18</strong></td>
<td>Patient ate an large amount of licorice which interacted with digoxin resulting in digoxin toxicity. The potential interaction between licorice and digoxin was not noted on the label.</td>
<td></td>
</tr>
<tr>
<td><strong>19</strong></td>
<td>She died due to a stroke</td>
<td></td>
</tr>
<tr>
<td><strong>20</strong></td>
<td>His anticonvulsant drug failed to control his seizures</td>
<td></td>
</tr>
<tr>
<td><strong>21</strong></td>
<td>Former drug abuser</td>
<td></td>
</tr>
<tr>
<td><strong>22</strong></td>
<td>Her mother and sister both had breast cancer</td>
<td></td>
</tr>
<tr>
<td><strong>23</strong></td>
<td>Indicated for in vivo diagnosis of Helicobacter pylori infection</td>
<td></td>
</tr>
<tr>
<td><strong>24</strong></td>
<td>Calcium supplement</td>
<td></td>
</tr>
<tr>
<td><strong>25</strong></td>
<td>Drug indicated for children aged 5 and older was given to infant, age 2 years</td>
<td></td>
</tr>
</tbody>
</table>

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**FDA CDER Perspective on MedDRA® Coding Quality in Safety Reports**
Overview of “MedDRA Data Retrieval and Presentation: Points to Consider” Document

MedDRA Data Retrieval and Presentation: Points to Consider

- An ICH-Endorsed Guide for MedDRA users on Data Output
- Developed by an ICH Expert Working Group
- Provides data retrieval and presentation options for industry or regulatory purposes
- Objective is to promote understanding of implications that various options for data retrieval have on accuracy and consistency of final output
Data Retrieval PTC
Points Addressed

• General Principles
  • Quality of Source Data
  • Documentation of Data Retrieval and Presentation Practices
  • Do Not Alter MedDRA
  • Organization-Specific Data Characteristics
  • Characteristics of MedDRA that Impact Data Retrieval and Analysis
  • MedDRA Versioning

• General Queries and Retrieval
• Standardised MedDRA Queries
• Customized Searches

Documentation of Data Retrieval and Presentation Practices

• Organization-specific guidelines
  • Consistent with Points to Consider documents
  • Coding conventions
  • Data retrieval and output strategies (including SMQs)
  • Quality assurance procedures
  • MedDRA version used for search
  • Search strategy methods
  • Version update processes
  • Processes for customized MedDRA queries
Quality of Source Data

- High quality data output is dependent on maintaining quality of original information reported by using consistent and appropriate term selection (Refer to MedDRA Term Selection: Points to Consider document)

Do Not Alter MedDRA

- Emphasized in term selection and data retrieval PTC documents.
Impact of MedDRA’s Characteristics – Grouping Terms

- HLGTs and HLTs provide clinically relevant groupings
  - HLGT Cardiac arrhythmias
    - HLT Cardiac conduction disorders
    - HLT Rate and rhythm disorders NEC
    - HLT Supraventricular arrhythmias
    - HLT Ventricular arrhythmias and cardiac arrest

Impact of MedDRA’s Characteristics – Grouping Terms (cont)

- Caution - ensure all terms are relevant to output
  - HLT Vascular tests NEC (incl blood pressure)
    - PT Blood pressure decreased
    - PT Blood pressure increased
- Caution - related PTs in different locations in SOC
  - HLT Bullous conditions
    - PT Stevens-Johnson syndrome
  - HLT Exfoliative conditions
    - PT Dermatitis exfoliative
Multi-Axiality

- Primary SOC allocation rules affect the way data are distributed across the terminology
- Impact on frequencies of medical condition of interest should be considered
- Example: for hepatic abnormality search in SOC Hepatobiliary disorders, SOC Investigations (laboratory test terms), SOC Surgical and medical procedures (e.g., PT Liver transplant)
- Main presentation is by Primary SOC; secondary SOCs used for alternate views

Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v16.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Infections and infestations</td>
<td>14 (31.8%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
### Secondary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v16.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>SOC Infections and infestations</strong></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported

### Secondary SOC Analysis – SOC Infections and infestations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v16.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>SOC Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>SOC Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
MedDRA Versioning

- MedDRA is updated twice a year
  - 1 March X.0 release (all levels)
  - 1 September X.1 release (LLT and PT levels only)
- Version used in data retrieval and presentation should be documented
- Resources:
  - “What’s New” document
  - Version report
- Terms used for queries should be in same version as data being queried

MedDRA Versioning - Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>MedDRA Version 15.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Pregnancy, puerperium and perinatal conditions</td>
<td>20</td>
</tr>
<tr>
<td>PT Anaesthetic complication foetal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 16.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Pregnancy, puerperium and perinatal conditions</td>
<td>0</td>
</tr>
<tr>
<td>SOC Injury, poisoning and procedural complications</td>
<td>20</td>
</tr>
<tr>
<td>PT Anaesthetic complication foetal</td>
<td></td>
</tr>
</tbody>
</table>
Developing Queries Using MedDRA

General Principles

- Define the medical condition
- Develop inclusion/exclusion criteria
- Know your data, e.g., how specific coding conventions impact retrieval strategy
- Good browser is key component
  - Flexible search capabilities
  - Ability to view secondary SOC assignments
Query Strategy Tips

- ALWAYS search the “non-multi-axial” SOCs
- Consider searching the “support” SOCs
- Use “Top-down” and “Bottom-up” searches
- Use multi-axial links
- Use grouping terms; exclude non-relevant PTs
- Avoid using LLTs in queries
  - Exception: for infections, specific species information is found at the LLT level

Connect the DOTSSSS!

- Diagnosis/disease terms
- Support SOCs (Other...)
- Signs & symptoms
- Social circumstances
- Operations (Surgical and medical procedures)
- Tests (Investigations)
Cardiac Failure

• Definition (from MedlinePlus http://www.nlm.nih.gov/medlineplus/ency/article/000158.htm)
  - Heart failure is a condition in which the heart cannot pump enough blood to the rest of the body
• Common symptoms are:
  - Cough
  - Fatigue, weakness, faintness
  - Loss of appetite
  - Need to urinate at night
  - Pulse that feels fast or irregular, or a sensation of feeling the heart beat (palpitations)
  - Shortness of breath when you are active or after you lie down
  - Swollen (enlarged) liver or abdomen
  - Swollen feet and ankles
  - Waking up from sleep after a couple of hours due to shortness of breath
  - Weight gain
Cardiac Failure (cont)

- Exams and Tests
  - Your health care provider will examine you for signs of heart failure:
  - Fast or difficult breathing
  - Leg swelling (edema)
  - Neck veins that stick out (are distended)
  - Sounds ("crackles") from fluid buildup in your lungs, heard through a stethoscope
  - Swelling of the liver or abdomen
  - Uneven or fast heartbeat and abnormal heart sounds
  - Many tests are used to diagnose, find the cause of, and monitor heart failure.
  - An echocardiogram (echo) is often the best test for heart failure. Your doctor will use it to guide your treatment.
  - Several other imaging tests can look at how well your heart is able to pump blood, and how much the heart muscle is damaged.

Cardiac Failure (cont)

- What happens next after the query is developed?
  - How do I use the query to retrieve cases from the database?
Standardised MedDRA Queries (SMQs)

Definition of SMQ

- Result of cooperative effort between CIOMS and ICH (MSSO)
- Groupings of terms from one or more MedDRA System Organ Classes (SOCs) related to defined medical condition or area of interest
- Included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to medical condition or area of interest
- Intended to aid in case identification
SMQ Benefits and Limitations

- **Benefits**
  - Application across multiple therapeutic areas
  - Reusable programming
  - Standardized communication of safety information
  - Consistent data retrieval
  - Maintenance by MSSO/JMO

- **Limitations**
  - Do not cover all medical topics or safety issues
  - Will evolve and undergo further refinement even though they have been tested during development

SMQ Development Summary

- Pre-release: tested on databases available to CIOMS Working Group members; typically, at least one company and one regulator database
- Production Phase: continue to be fine-tuned by MedDRA subscribers through the MSSO maintenance process
SMQs in Production - Examples

- 截止到第 16.0 版, 总共有 90 个SMQs (Other SMQs in development)
  - 粒细胞缺乏症
  - 过敏性反应
  - 脑血管疾病
  - 惊厥
  - 抑郁症和自杀/自伤
  - 肝脏疾病
  - 缺血性心脏病
  - 缺乏疗效/效果
  - 周围神经病变
  - 妊娠和新生儿主题
  - 伪膜性结肠炎
  - 横纹肌溶解症/肌病
  - 严重的皮肤不良反应
  - 系统性红斑狼疮

Narrow and Broad Searches

- “Narrow” scope – specificity (cases highly likely to be condition of interest)
- “Broad” scope – sensitivity (all possible cases)
- “Broad search” = All broad + all narrow terms
- MedDRA term can be broad or narrow depending on SMQ
  - Example: PT Renal failure acute
    - Narrow in Acute renal failure (SMQ)
    - Broad in Rhabdomyolysis/myopathy (SMQ)
**Narrow vs. Broad Example**

### Lactic acidosis (SMQ)

**Definition**
Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsic cardiac contractility may be depressed, but intramyocardial function can be normal because of catecholamine release. Peripheral arterial vasodilation and central vasoconstriction can be present. Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may occur. Characterized by an increase in plasma lactate. Acidosis is confirmed with a blood lactate of over 5 mmol/L. Clinical presentation in type B lactic acidosis: Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain. Course of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness.

**Source**

**Note**
Testing in two regulatory databases confirmed that the term list is adequate, in one regulatory database, the term "acidosis" identified cases, but this may be a phenomenon of the database characteristics (coding of assigning to terms of an older terminology or other coding conventions).

---

### Algorithmic SMQs

- Some SMQs are designed to utilize algorithms
- Better case identification among broad search terms may result if cases are selected by a defined combination of selected terms
Algorithmic SMQ Example

- **Anaphylactic reaction (SMQ):**
  - A case with any of the following PTs:
    - Anaphylactic reaction
    - Anaphylactic shock
    - Anaphylactic transfusion reaction
    - Anaphylactoid reaction
    - Anaphylactoid shock
    - Circulatory collapse
    - First use syndrome
    - Kounis syndrome
    - Shock
    - Type I hypersensitivity
  
  (Narrow search terms = Category A)

---

Algorithmic SMQ Example (cont)

<table>
<thead>
<tr>
<th>Category B - Upper airway/ Respiratory</th>
<th>Category C - Angioedema/ Urticaria, etc.</th>
<th>Category D - Cardiovascular/ Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Allergic oedema</td>
<td>Blood pressure decreased</td>
</tr>
<tr>
<td>Asthma</td>
<td>Angioedema</td>
<td>Blood pressure diastolic decreased</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Erythema</td>
<td>Blood pressure systolic decreased</td>
</tr>
</tbody>
</table>

- Case = A (Narrow terms)
- Or Term from Category B and term from Category C
- Or Term from **either** Category B or Category C **plus** Term from Category D
Hierarchical SMQs

- Some SMQs have been developed as a set of queries related to one another in a hierarchical relationship
- Not related to MedDRA standard hierarchy
- One or more subordinate SMQs combined to create a superordinate, more inclusive SMQ

Hierarchical SMQ Example

- Haematopoietic cytopenias
  - Erythropenia
  - Leukopenia
  - Thrombocytopenia
  - Cytopenia and haematopoietic disorders affecting more than one type of blood cell
Other Data Included in SMQ Files

- Description field
  - Additional information about each SMQ (from SMQ Introductory Guide)
- Source field
  - Medical references used in development/maintenance
- Development note
  - Pertinent notes for proper use
  - Description of algorithm (if applicable), and definition of categories

SMQ Files and Documents

- MedDRA distributed files unchanged by inclusion of SMQ files
- SMQ Introductory Guide
  - Recommended reading for optimal utilization of SMQs
  - Details of individual SMQs
  - Notes for implementation and/or expectation of results
- Production SMQ Spreadsheet
  - SMQs and included terms (.xls)
- “What’s New” document summarizes SMQ changes
- Original CIOMS Working Group documentation
How to “run” SMQs

SMQ Versioning

- Examples of PTs added to SMQs in MedDRA Version 16.0:
  - PT *Dystonic tremor* in SMQ *Dystonia*
  - PT *Pulmonary endarterectomy* in SMQ *Embolic and thrombotic events, arterial*

- Using version 15.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 16.0
SMQ Applications

• Clinical trials
  - Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
  - Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)
• Postmarketing
  - Selected SMQs to retrieve cases for suspected or known safety issue
  - Signal detection (multiple SMQs employed)
  - Single case alerts
  - Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)

Browser Demonstration
SMQ View
MedDRA and Signal Detection

Influence of the MedDRA® hierarchy on pharmacovigilance data mining results


MedDRA and Signal Detection (cont)

• Methodology
  - Data mining using three algorithms for signals of disproportionate reporting (SDRs) for 26 drugs in FDA’s AERS database
  - Adverse events identified by PTs, HLTs, or SMQs

• Conclusions
  - HLTs and SMQs can improve % of unlabeled supported SDRs in data mining
  - Improvement holds for all algorithms tested
  - Trade-off: HLTs, SMQs medically less-specific vs. PTs
  - Need to examine component PTs of each HLT or SMQ that results in an SDR
Customized Searches

“Modified MedDRA Query Based on an SMQ”

- Do not modify SMQ unless there is a compelling reason – makes it non-standard
- All modifications must be documented
- Version updates and maintenance are responsibility of organization that created it
Customized Searches – Ad Hoc Queries

- Need medical knowledge
- Need knowledge of structure and characteristics of MedDRA and of your data
- Refer to Data Retrieval and Presentation: Points to Consider document for query construction tips
- Save query for future use; maintenance needed for MedDRA version changes
- Consider submitting *ad hoc* query to MSSO via change request for possible development as an SMQ

FDA CDER Approach to MedDRA® Search Strategies for Signal Detection
MedDRA Versioning

MedDRA Term Selection: PTC

- MedDRA Term Selection: Points to Consider.
  - Section 4.1. Versioning
    - 4.1.1 Versioning methodologies
    - 4.1.2 Timing of version implementation
Versioning Methodologies

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Resource Intensity</th>
<th>Data Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Begin to use new version for coding new data; no recoding of existing data</td>
<td>Least</td>
<td>Least</td>
</tr>
<tr>
<td>2</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches and Recode verbatim terms to new LLTs that are more accurate concepts</td>
<td>Most</td>
<td>Most</td>
</tr>
</tbody>
</table>

Timing of Version Implementation

A new release version of MedDRA should become the reporting version on the first Monday of the second month after it is released. To synchronize this event over the three ICH regions, the MSSO recommends midnight GMT, Sunday to Monday, for the switchover. For example:

- 1 March - MedDRA X.0 released
- First Monday of May - MedDRA X.0 becomes the reporting version
- 1 September - MedDRA X.1 released
- First Monday of November - MedDRA X.1 becomes the reporting version
MedDRA Version Analysis Tool (MVAT)

• Via “Downloads” page on MSSO Web site, or at https://mssotools.com/mvat/

MVAT Homepage

• Tool has three modules:
  ♦ Version Report Generator
  ♦ Data Impact Report
  ♦ Search Term Change
Version Report Generator

- New LLTs (including new PTs)
- New PTs
- Promoted LLTs
- Demoted PTs
- LLTs under different PTs
- LLT (excl PTs) Primary SOC Changes
- PT Primary SOC Changes

Results can be exported to spreadsheet

Version Report Generator (cont)

![Summary & Details]

Click on “Details”…
Version Report Generator (cont)

<table>
<thead>
<tr>
<th>Promoted LLT Code</th>
<th>Promoted LLT</th>
<th>13.0 PT Code</th>
<th>13.0 PT</th>
<th>14.1 Primary SOC Code</th>
<th>14.1 Primary SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>10051124</td>
<td>Hyperfibrinogenaemia</td>
<td>10020006</td>
<td>Hypercoagulation</td>
<td>10005529</td>
<td>Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>10067520</td>
<td>Hyperprothrombinaemia</td>
<td>10020006</td>
<td>Hypercoagulation</td>
<td>10005529</td>
<td>Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>10058516</td>
<td>Hyperthrombinaemia</td>
<td>10020008</td>
<td>Hypercoagulation</td>
<td>10005520</td>
<td>Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>10051125</td>
<td>Hypochromogenaemia</td>
<td>10020073</td>
<td>Hycoaguable state</td>
<td>10005329</td>
<td>Blood and lymphatic system disorders</td>
</tr>
</tbody>
</table>

Search Term Change

- Allows user to search individual terms or MedDRA codes for changes that occurred between any two MedDRA releases
Search Term Change (cont)

Data Impact Report

Upload PT or LLT terms and/or codes; generates a set of reports specific to the input:

- Promoted LLTs
- Demoted PTs
- LLTs under different PTs
- LLT (excl PTs) Primary SOC Changes
- PT Primary SOC Changes
- MedDRA LLT and PT Text Changes
- MedDRA Code Switches
- Currency Changes
- Hierarchy Changes
Data Impact Report (cont)

**Data Impact Report**

**MedDRA Version** | **Import Data** | **Data Validation**
---|---|---

**Select MedDRA**

**Starting Version (your data was coded):**
MedDRA 14.0 English

**Ending Version (you are interested in):**
MedDRA 14.1 English

*Note: The starting MedDRA version must be older than the ending MedDRA version.*

Next >>>

---

Data Impact Report (cont)

**MedDRA Version** | **Import Data** | **Data Validation**
---|---|---

**Load Your Data**

Your data must be in Microsoft Office Excel format. The first row must contain a column header, data must begin from the second row. The required column sequence is Row ID, LLT/PT Term, LLT/PT Code. Supply either LLT/PT Term information, LLT/PT codes, or both. Row ID information is optional. The following is an example:

<table>
<thead>
<tr>
<th>Row ID</th>
<th>LLT/PT Term</th>
<th>LLT/PT Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC0000 (optional)</td>
<td>Adenoma benign NOS</td>
<td>1001034</td>
</tr>
</tbody>
</table>

**Notes:**

- The MedDRA version of the imported data should match the MedDRA starting version.
- iVAT does not store your data. Your data will be erased after generating the data impact report.
- The maximum number of records accepted is 10,000.
- The data impact report assumes the uploaded data are existing MedDRA terms; therefore new term information is not included. Also, Complex Change and SMQ changes are not included.

Select data file (*.xlsx, *.xls, *)

Browse

Next >>> Cancel

---
Data Impact Report (cont)

Click on “Impact Details”...

Data Impact Report (cont)

<table>
<thead>
<tr>
<th>Demoted PT Code</th>
<th>Demoted PT</th>
<th>14.1 PT Code</th>
<th>14.1 PT</th>
<th>Row ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>10006430</td>
<td>Chemistry abnormal</td>
<td>10023547</td>
<td>Laboratory test abnormal</td>
<td>4</td>
</tr>
<tr>
<td>10043497</td>
<td>Therapeutic agent poisoning</td>
<td>10070863</td>
<td>Toxicity to various agents</td>
<td>13</td>
</tr>
<tr>
<td>10001348</td>
<td>Adrenal disorder NOS</td>
<td>10031347</td>
<td>Adrenal disorder</td>
<td>22</td>
</tr>
<tr>
<td>10001490</td>
<td>Agitation aggravated</td>
<td>10001497</td>
<td>Agitation</td>
<td>30</td>
</tr>
<tr>
<td>10002010</td>
<td>Amputation NOS</td>
<td>10061827</td>
<td>Amputation</td>
<td>43</td>
</tr>
<tr>
<td>10003143</td>
<td>Aterial aneurum NOS</td>
<td>10002320</td>
<td>Aneurym</td>
<td>69</td>
</tr>
</tbody>
</table>
MVAT Resources

- MVAT videocast
  - Recorded streaming videocast, in Windows Media Format (.wmv):
  - Videocast can also be downloaded
- MSSO Help Desk for general and technical questions: [mssohelp@mssotools.com](mailto:mssohelp@mssotools.com)
- MVAT FAQs:

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MVAT FAQs

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**MedDRA Version Analysis Tool (MVAT) FAQs**

- **What is MVAT?**
- **Who may access MVAT?**
- **Does MVAT support non-English languages?**
- **Do I need a username and password for MVAT?**
- **Does the MSSO provide training for MVAT?**
- **Is there an MVAT user guide?**
- **What computer platforms is MVAT compatible with?**
- **Where do I go if I need help using MVAT?**
- **How does the new version of MedDRA get loaded into MVAT?**
- **Will the MSSO continue to produce the Version Report?**
- **What is the data impact report?**
- **How does the MVAT data impact report handle my uploaded MedDRA terms?**
- **Where should I report any errors when using MVAT?**
- **Can more than one user from an organization be logged on at the same time?**

**Find these FAQs on the MSSO Web page:**
LEARNING OBJECTIVE: Review the various strategies for retrieval and subsequent analysis of MedDRA-coded data in clinical safety and pharmacovigilance

- In this tutorial we have:
  - Learned about the ‘MedDRA Data Retrieval and Presentation: Points to Consider’ document and reviewed various options for data retrieval for industry and regulatory purposes
  - Reviewed data quality issues
  - Learned about Standardised MedDRA Queries
  - Discussed customized searches
Tutorial Summary (cont)

LEARNING OBJECTIVE: Discuss the issues relating to MedDRA versioning

• In this tutorial we have:
  ◦ Considered how MedDRA versioning affects data analysis
  ◦ Discussed the implementation of the BRP recommendations
    ▪ Versioning methodologies
    ▪ Timing of version implementation
    ▪ Development of a versioning tool

谢谢！